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E: ISSN NO.: 2455-0817 *Remarking An Analisation*

Synthesis and Pharmacological Screening of Novel Substituted Pyrimido Thiazin-4(6H)-One Derivatives

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Abstract

The starting material 2-acetylnaphtho [2, 1-b] furan has been synthesized by literature (Stoermer& Schaffer) method. It is then converted in to a series of substituted chalcones (2a-f) were prepared by Claisen-Schmidt condensation with substituted aromatic aldehyde. These chalcones on reaction with thiourea in presence of ethanol and concentrated hydrochloric acid gave their corresponding thiopyrimide derivatives (3a-f), subsequent treatment with 3-bromopropionic acid and anhydrous sodium acetate yields the title compounds. The antimicrobial screening showed that many of these obtained compounds have good activity against bacteria and fungi comparable to and as reference drugs.

Keywords: Naphthofuran, Chalcones, Thiopyrimidine, Antimicrobial

Introduction

Heterocyclic compounds occues very widely in nature and are essential to life. Importance of Naphthofuran derivatives as biologically, pharmacologically and Industrially important molecules [1,2]. And are well known for various types of biological activities like antifertility, growth inhibitory, antitumor [3, 4]. The Naphthofuran derivatives have been shown to exhibit cytotoxic activity [5] keeping these reports in view and in constitution of our search for more potent Naphthofuran derivatives [6-9] pyrimidine based heterocyclic compounds are of interest as potential bioactive molecules and exhibit analgesic [10] , antiviral[11], antipyretic[12] and anti-inflammatory [13, 14] activity. Recently two PCT international applications have been found for 2-thopyrimidine derivatives possessing potent activity against inflammation and immune disorders [15-18]

Aim of the Study

In view of this observation and in continuation of our previous work (19-21) in heterocyclic chemistry. We synthesized some new thiopyrimidine and thiazin-4(6H)-one derivatives using substituted chalcones and it was tested for their antimicrobial activity.

Experimental

Melting points were determined in open capillary method and are uncorrected. IR spectra were recorded in KBr on Bruker FT-IR (Alpha-p)^{1}H NMR spectra on Bruker "AVANCE 400" MHz spectrometer using TMS as an standard, (chemical shifts in ðppm) and mass spectrum on Shimadzu GCMS QP 5050A. Japan model-DI mass spectrometer operating at 70ev.Progress of the reaction was monitored by TLC. The entirecompounds have been recrystallized from ethanol.

Synthesis of 2-Acetyl naphtho [2, 1-b] furan (1)[8]

A 250 ml 4-necked round bottom flask fitted with overhead mechanical stirrer, a dropping funnel, and a thermometer and reflux condenser with chilled water circulation. Flask was charged with 2-hydroxy-1-naphthaldehyde (17.80 gm, 0.10 mol),chlorocacetone (10.75 gm, 0.11 mol) and anhydrous potassium carbonate (15 gm, 0.11 mol) were refluxed in dry acetone. (75mL) for 12 h. Potassium salt were filtrate on removed of solvent and on trituration with ethanol gave the pale yellow crystals of 2-acetyl naphtho [2, 1-b] furan (1). The sample was purified by absolute ethanol. M.P.96^{0}C yield 60%.

Typical experimental procedure for synthesis of 3-(4-hydroxyphenyl)-1-(naphtho [2, 1-b] furan -2yl) prop-2-en-one (2a-f)

Flask was charged with mixture of 2-acetylnaphto [2, 1-b] furan (4.20 gm,0.02 mole) (1) and p-hydroxybenzaldehyde (2.68 gm, 0.022 mol). It was stirred in ethanol (50 mL) and then potassium hydroxide (50%)

(10ml) was added portion wise, keeping the temperature below 10^0C throughout the addition. The mixture was kept for 36 hr at room temp., after completion of reaction, reaction mixture was poured into crushed ice and the solid obtained was filtered under vacuum. It was washed firstly with sodium carbonate solution and then with water, dried and the product was recrystallized from ethanol to afford the pure product in 60-70% yield (2c). Same procedure is extended for other compounds of this series (2a-f) were synthesized by using appropriate aldehyde.

Spectral discussion

1. Compound 2C:**IR (KBr, vcm^{-1})** 3310 cm^{-1}(Ar-o-H str.), 3058 cm^{-1}(-CH str. of. Ar), 1644 cm^{-1}(C=0 str. in ketone),1586 cm^{-1}(C=C str.) 1515 cm^{-1} (C=C str. in Ar), 1443 and 1359 cm^{-1} (CH_3 def.), 1153 and 1167 cm^{-1} (C-O-C str) 830 cm^{-1} (-CH str.) 747 cm^{-1} (Ar-H-opb)
2. **^{1}H NMR ($CDCl_3$ in δpmm)** 6.35(d,lH-CO-CH), 6.95(d,lH, C=CH),7.21-8.24 (complex m, 11 H, Ar-protons), 10.32 (s,1H, phenolic-OH) proton
3. **Mass (m/z)** : 314[M]$^+$, 221, 195, 147, 119, 118, 91, 69, 65, 43

Synthesis of 3,4-dihydro-6-(naphtho[2, 1-b]furan -2-yl)-4-phenyl pyrimidin-2(1H) thione (3a-f)

A mixture of 1-(naphtho[2, 1-b]furan-2-yl)-3-phenyl prop-2-en-one-(2.98gm, 0.01 mole) (2a) and thiourea (1.52gm,0.02 mole) were dissolved in dry ethanol (50ml) concentrated HCL (10mL) was added and refluxed for 18 h with constant stirring. The progress of the reaction was monitored by TLC. After completion of reaction, it was filtered while hot and allowed to cool then neutralized with 5N sodium hydroxide solution. The resulting solid was washed well with water (25mL× 3) dried and the product was recrystallized from acetic acid to obtain (3a). Compounds (3b-f) were prepared similarly from (2b-f). The physical data of the thiopyrimidine are shown in table- 1

Spectral Discussion

Compound (3a)

IR(KBr,vcm^{-1}), 3426(N-H str.), 3062(C-H), 2922(C-H str. in -CH_2), 2431(S-H str.C=S),1628(C=N str.), 1380(C=S str) [19] 1074-1109 (-C-O-C str)

^{1}H NMR ($CDCl_3$ in δppm)

3.98 (d, lH, proton of position 1), 3.41(d, lH, proton of position 3), 3.86(d, lH, proton of position 4), 5.81(d, lH, proton of position 5), 6.90-8.30(m,12 H, Ar-protons)

Mass

(m/z) 356 (m$^+$), 195, 194, 115, 105, 103, 94, 93, 91, 77, 70, 66, 65, 55, 44

Synthesis of 6-(substituted)-2,3-dihydro-8-(naphtho[2,1-b]furan-2-yl)pyrimido[2,1-b][1,3]thiazin-4(6H)-one (4a-f)

A mixture of substituted thiopyrimidine (3a-f)0.011 mmol) and 3-bromopropionic acid and bromoacetic acid (1 mmol) was dissolved in 50mL mixture of AcOH/Ac_2O (1:3) in presence of 3 gm of anhydrous sodium acetate was refluxed for 8-9 h. The reaction mixture was cooled and poured on to cold water with stirring; the solid formed was filtered and recrystallized to give corresponding title compounds (4a-f).

Spectral Discussion

Spectral analysis of 6-(4-chlorophenyl)-2,3-dihydro-8-(naphtho[2,1-b]furan-2-yl)pyrimido[2,1-b][1,3]thiazin-4(6H)-one (4e)

Compound (4e): **IR (KBr,vcm^{-1})**

1720 (C=O), 3430 (N-H str.), 3055(C-H str.), 2882 (C-H str. in CH_2), 1034-1121 (C-O-C str).

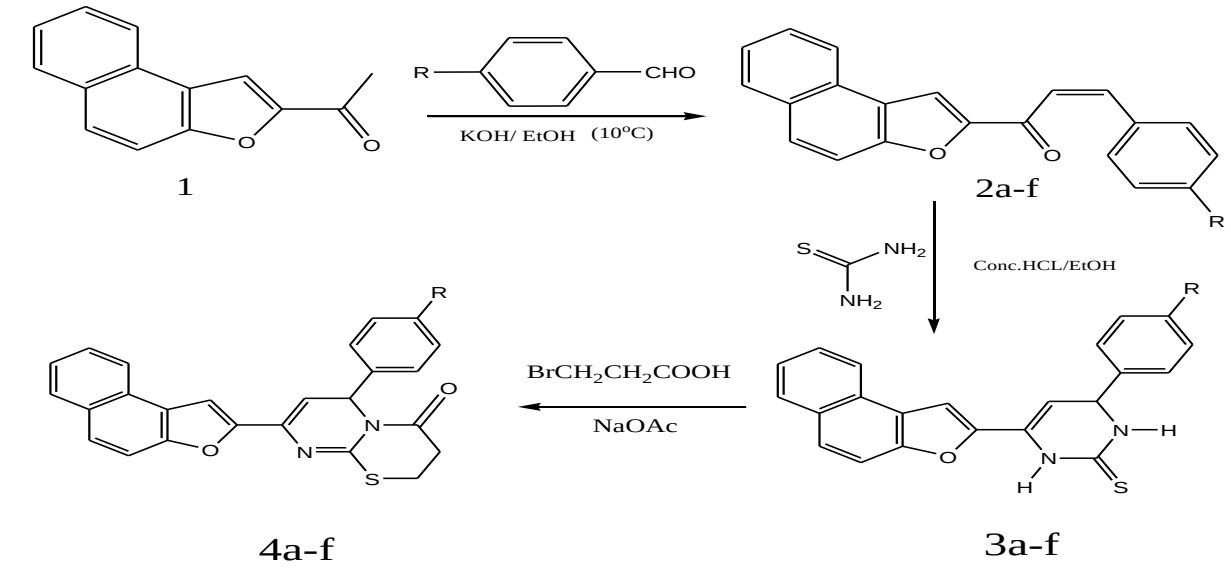
^{1}H NMR (4e) ($CDCl_3$ in δppm)

3.38 (t, 2H, C-2 protons), 2.91 (t, 2H, C-3 protons), 5.86(d, 1H, C-6 proton), 6.89(d, 1H, C-7 proton), 6.90-7.70(m, 11 H, Ar-protons)

Mass

(m/z) 444 [M]$^+$

Reaction Scheme



Where-R=H,CH_3,OH,OCH_3,Cl&F

Table 1: Physical and Characterization Data of the Synthesized Compounds

Comp	Molecular formula	Mol.wt.	Yield	M.P. ℃	Elements % calc (found)				
					C	H	N	S	X
4a	$C_{25}H_{18}N_2O_2S$	410	52	280	73.15(**72.15**)	4.42(**4.0**)	6.82(**5.0**)	7.81(**7.80**)	-
4b	$C_{26}H_{20}N_2O_2S$	425	60	240	73.56(**73.00**)	4.75(**4.60**)	6.60(**6.50**)	7.55(**7.50**)	-
4c	$C_{25}H_{18}N_2O_3S$	426	58	260	70.40(**71.10**)	4.25**4.20**)	6.57(**6.40**)	7.52(7.**40**)	-
4d	$C_{26}H_{20}N_2O_3S$	440	65	282	70.89(**71.10**)	4.58(**4.10**)	6.36(**6.0**)	7.28(**7.30**)	-
4e	$C_{25}H_{17}ClN_2O_2S$	444	63	>300	67.49(**65.50**)	3.85(**4.0**)	6.30(**6.20**)	7.21(**7.0**)	7.97(**8.00**)
4f	$C_{25}H_{17}FN_2O_2$	428	62	>300	70.08 (69.10)	4.00 (3.8)	6.54 (6.50)	7.48 (7.20)	4.43 (4.50)

Table 2: Antimicrobial Activity of Synthesized Compound

Comp	Antibacterial Activity (Zone of Inhibition in mm)				Antifungal Activity			
	E.coli	***S.typhi***	***S.aureus***	***B.substilis***	***A.niger***	***P.chryso-genum***	***F.monelifor me***	***C.albicans***
4a	12	17	16	19	+ve	+ve	+ve	-ve
4b	14	18	28	22	-ve	+ve	+ve	+ve
4c	16	17	23	20	+ve	+ve	+ve	+ve
4d	14	18	30	23	+ve	+ve	+ve	-ve
4e	10	11	09	07	-ve	-ve	+ve	-ve
4f	12	09	11	21	-ve	+ve	+ve	-ve
Pencillin	18	20	32	28	-	-	-	-
Griseofu-lvin	-	-	-	-	+ve	+ve	+ve	+ve

Result and Discussion

In this context we have reported that the facile synthesis of different 6-(substituted)-2,3-dihydro-8-(naphtho[2,1-b]furan-2-yl)pyrimido[2,1-b][1,3]thiazin-4(6H)-one derivatives in moderate to good yields.We hope this methodology will be helpful for further synthesis of different thiazin-4(6H)-one derivatives for pharmaceutical use. In the antimicrobial study, filter paper; disc diffusion plate method was employed to evaluate the antimicrobial activity [20]. The zone of inhibition was compared with the standard drug. (Penicillinfor bacteria and Griseofulvin for fungi). Results are summarized in Table 2.Investigation of antimicrobial activity revealed that the compounds (4a-f) showed significant antibacterial activity when compared with standard drug penicillin. However the compounds (4b, 4c,4d) were found to be more potent on all the bacterial strain. Compound (4a-f) showed significant antifungal activity when compared with standarddrug Griseofulvin. Compound (4a, 4b,4c, 4d) showed good antifungal activity.This result clearly revealed the contribution of electron releasing groups on the aromatic ring in enhancing the microbial activity.

Endnotes

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